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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,820	10/12/1999	DANIEL G. CHAIN	20555/1203301-US1	6495

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EXAMINER	
DUFFY, PATRICIA ANN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/402,820	CHAIN, DANIEL G.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,23,24,33,35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14, 23, 24, 33, 35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2x2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-31-07 has been entered.

The amendment filed 10-31-07 has been entered into the record. Claims 1-13, 15-22, 25-32, 34, and 36-37 have been cancelled. Claims 14, 23, 24, 33, 35 and 38-40 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Maintained

Claims 14, 24 and 39 stand are rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Vigo-Pelfrey et al (Journal of Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) is maintained for reasons made of record.

The claim is drawn to a monoclonal antibody that is free-end specific for the free n-terminus of an amyloid beta peptide binds to said free N-terminus said free terminus and does not bind to the amyloid beta-precursor protein from which said amyloid beta peptide may be proteolytically derived wherein the amyloid beta peptide is soluble in cerebrospinal fluid. The claim is also drawn to a neutralizing antibody that binds soluble amyloid beta.

Saido et al teach a polyclonal antibody 9204, that was produced using a synthetic heaxamer peptide DAEFRC (Asp-Ala-Glu-Phe-Arg-Cys) conjugated to keyhole limpet hemocyanin. The antibody distinguished the fragments possessing the exact amino terminus of AB from the intact precursors and other fragments including the secretase products. Antibody 9204 also recognized synthetic AB1-40 peptide but not AB2-40 peptide. Furthermore, Saido et al teaches that binding of antibody 9204 to AFF-C100 was inhibited by the haptenic peptide DAEFRC, but not by MADEFTC or by AEFRHC. Saido et al teaches that this indicates that the antibody has strict specificity toward the cleavage site with an accuracy of 1 amino acid residue (i.e. the instant free-end specific N-terminal specific). Saido et al teaches that the use of the cleavage site specific antibody provides for better relative quantitativeness. (see page 15254-55, column 1, Resultes, first and second paragraphs). Saido et al teaches that "similar approaches for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxyl-terminal processing of AB peptides...". Saido et al differs by not teaching a monoclonal antibody with the properties of polyclonal antibody 9204.

Takeda teaches that monoclonal antibodies that are specific for the N-terminal and C-terminal of AB are useful for the detection of AB1-40 and AB1-42 for the detection of AB species i*n vitro* (see page 5) Takeda teaches that AB1-40 is water soluble (page 4, lines 33-41). Takeda teach the N and C-terminal peptide sequence of AB1-40.

Vigo-Pelfrey et al teach the specific structures of beta amyloid peptides from human cerebrospinal fluid (CSF). Vigo-Pelfrey et al teach that amino acid sequencing reveals species of amyloid beta with N-termini of Asp1, Glu3, His6, Glu11 and Val12. Laser desprption mass spectrometry confirmed the presence of amyloid beta species containing 27, 28, 30, 34, 35, 40, 42 and 43 amino acids all beginning at Asp1. Vigo-Pelfrey et al is seen to teach the soluble amyloid beta species present in human CSF. Vigo-Pelfrey et al is seen to teach the free end C-terminus terminus of AB1-40 is present and soluble in CSF.

Goding teaches routine methods of making monoclonal antibodies with defined immunogens.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to use the teachings of Saido et al to generate free-end N-terminal specific antibodies that do not bind the prescursor and bind species of soluble amyloid beta found in human cerebrospinal fluid using the conventional techniques of Goding et al because of the well established advantages of high-affinity, high specificity and unlimited supply that are central to monoclonal antibodies. One would have been motivated to make monoclonal antibodies to decrease the lot to lot variability that can happen with polyclonal antisera and Takeda et al teach that the monoclonal antibodies are useful for the detection of AB1-40 and AB1-42 for the detection of AB species *in vitro* and that AB1-40 is water soluble and present in the human cereprospinal fluid. One of ordinary skill in the art would have a reasonable expectation of success given the demonstrated immunogenicity of the epitope. With respect to neutralizing antibody claims, the soluble form of amyloid beta is known in the art to be non-toxic (i.e. not neurotoxic) and as such any antibody that binds has neutralizing function since the anitboody binds a non-toxic form of amyloid (i.e. soluble).

Applicant's arguments have been carefully considered but are not persuasive. Applicant argues that the cited prior art fails to teach or suggest and antibody that binds soluble amyloid beta. This is simply not so. Takeda et al teach that their antibodies are useful for detecting amyloid beta in cerebrospinal fluid and Vigo-Pelfry et al teach that the specific structures of soluble amyloid beta in the cerebrospinal fluid. Applicants argue that merely because the antibody is raised to a particular structure and binds soluble amyloid beta and cites 2005/0124016 that reaches different conformations depending upon soluble, non-fibrillar and or/oligomeric. This is not persuasive because the art at the time of filing classified the specific structures of Vigo-Pelfrey as soluble. The existance of soluble beta amyloid was present in the art long before Applicants filed this

Application as evidenced by Schenk et al US Patent 5,593,846 and antibodies thereto were known. The art methodology that generated that antibodies of the '846 patent that bind the soluble amyloid of the art is no different than that as combined and as such, the skilled artisan would expect that art as combined to bind an amyloid beta peptide soluble in cerebrospinal fluid. As to no explicit teaching or suggestion, the desirability of end-specific antibodies that discriminate and bind diagnostically relevant amyloid beta peptides is well established in the art. The soluble amyloid beta peptides were known, the end amino acid sequences were known and as such the monoclonal antibodies that are free-end specific are obvious. The suggestion test is not a rigid categorical rule. The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999). As held in Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1472 (Fed. Cir. 1997), "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

Applicants argue that Saido et al is not concerned with therapeutic benefits of targeting amyloid beta but with spatial resolution and it is of no consequence to Saido A whether specific forms of amyloid beta are detected and the remaining references do not cure this deficiency. This is not persuasive because the references as a whole do not have to teach the identical problem or benefit. It is what the references as a whole teach. Rationale different from Applicant's is permissible. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter,* 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). Applicants argue and provide evidence

that antibodies detect soluble and insoluble forms of amyloid beta with different specificities. It is noted Applicants improperly use the term specificities as meaning different affinities and indicate antibody A and antibody B have different affinities toward different forms of amyloid beta. Different affinities are not different specificities. The method of making and binding of the antibodies of the Exhibit 6 and 7 are not set forth and not accompanied by details in a sworn declaration. Further, the claims do not exclude binding to non-soluble forms. It was well established in the art at the time the invention was made that antibodies raised to one polypeptide would also specifically bind other polypeptides sharing the epitope recognized by the antibody. For example, Bost et al. (Immunol. Invest. 1988; 17:577-586) teach that an antibody specifically bound an epitope shared by two different polypeptides, but did not bind irrelevant peptides not sharing this epitope. The epitope was determined to be a homologous sequence in the two proteins in which 4 of 6 residues were identical (see entire document, but especially the Abstract, Discussion, and "Results", page 579). Similarly, Bendayan (J. Histochem. Cytochem. 1995; 43:881-886) characterized the specific reactivity of a monoclonal antibody produced to human proinsulin and showed that although the antibody was highly specific, it bound to not only human proinsulin, but to proinsulin from other species (see entire document). The fact that Antibody A of Exhibit 6 and Antibody B bind both the soluble and fibrillar forms, does not change the epitope to which the antibody binds. That is the specificity is identical for the antibodies, but the affinity is different. Applicants do not define antibody specificity as having particular affinities and neither does the prior art and reliance on such is not persuasive. Antibody specificity is defined by the epitope to which the antibody binds. No particular affinities are recited in the claims. Collectively, the art directs one to monoclonal antibodies that bind free-N or C-terminus of soluble amyloid beta. Applicants argue that the references do not teach antibodies that are specific for soluble form of amyloid beta. This is not persuasive as set forth "specific" does not exclude binding to the non-soluble form. Since

specificity is discussed with respect to "end-specific" and not specific to soluble or aggregated forms Applicants arguments with regard to this interpretation are not persuasive. Applicants argue that the antibody has to be specific for soluble amyloid beta. The fact that the antibodies may also bind insoluble or fibrillar amyloid does not make the antibody any less specific. Specificity is determined by the antibody combining site and the epitope to which it binds. The fact that soluble amyloid and fibrillar amyloid have the same epitope does not make that antibody any less "specific". The specification does not discuss "specificity" with respect to "soluble", only "end-specific". As such, the non-conventional argued interpretation of specificity is not persuasive. Applicants again argue that there is not teaching suggestion or motivation to make antibodies to soluble beta amyloid. This is not persuasive for all the reasons already made of record. The courts have held "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). Finally, an obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). In the instant case the soluble amyloid beta peptides were known, the technology was known, it is routine to screen for antibodies with the desired specificity.

Claims 14, 33 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) in view of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal of Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B), Vigo-Pelfrey et al (Journal of Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97).

The claims are drawn to a monoclonal antibody that is free-end specific for the free C-terminus of an amyloid beta peptide 1-40 wherein the antibody binds to said free C-terminus said free terminus and does not bind to the amyloid beta-precursor protein from which said amyloid beta peptide may be proteolytically derived wherein the amyloid beta peptide is soluble in cerebrospinal fluid.

Takeda teaches that monoclonal antibodies that are specific for the N-terminal and C-terminal of AB petides are useful for the detection of AB1-40 and AB1-42 for the detection of AB species i*n vitro* (see pages 4-5). Takeda teaches that AB1-40 is water soluble (page 4, lines 33-41). Takeda teach the N and C-terminal peptide sequence of AB1-40. Takeda teach the monoclonal antibody BA-27a, that was considered to be specific for the C-terminus of beta amyloid (1-40), and weakly cross-reacted to beta-amyloid (1-38), (1-39) and beta amyoid (1-42) with a cross reactivity with 2% or less (page 34, lines 41-46). Takeda et al differs by not teaching a monoclonal antibody that has no cross-reactivity as "uniquely recognizes" the free C-terminal of AB1-40 and does not recognize the precursor.

Saido A teaches a polyclonal antibody 9204, that was produced using a synthetic heaxamer peptide DAEFRC (Asp-Ala-Glu-Phe-Arg-Cys) conjugated to keyhole limpet hemocyanin for the N-terminal of AB1-40. The antibody distinguished the fragments possessing the exact amino terminus of AB from the intact precursors and other

fragments including the secretase products. Antibody 9204 also recognized synthetic AB1-40 peptide but not AB2-40 peptide. Furthermore, Saido et al teaches that binding of antibody 9204 to AFF-C100 was inhibited by the haptenic peptide DAEFRC, but not by MADEFTC or by AEFRHC. Said o et al teaches that this indicates that the antibody has strict specificity toward the cleavage site with an accuracy of 1 amino acid residue (i.e. the instant free-end specific N-terminal specific). Saido et al teaches that the use of the cleavage site specific antibody provides for better relative quantitativeness. (see page 15254-55, column 1, Results, first and second paragraphs). Saido et al teaches that "similar approaches for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxyl-terminal processing of AB peptides…". Saido et al teach that their unique methodology for producing such proteolytic produce-specific antibodies now seems to have general applicability (page 15254 (column 1, see first paragraph results section).

Saido B teaches a general technique for producing antibodies that specifically distinguish a proteolyzed form from a given intact form and are free-end specific.

Vigo-Pelfrey et al teach the specific structures of beta amyloid peptides from human cerebrospinal fluid (CSF). Vigo-Pelfrey et al teach that amino acid sequencing reveals species of amyloid beta with N-termini of Asp1, Glu3, His6, Glu11 and Val12. Laser desprption mass spectrometry confirmed the presence of amyloid beta species containing 27, 28, 30, 34, 35, 40, 42 and 43 amino acids all beginning at Asp1. Vigo-Pelfrey et al is seen to teach the soluble amyloid beta species present in human CSF. Vigo-Pelfrey et al is seen to teach the free end C-terminus terminus of AB1-40 is present and soluble in CSF.

Goding teaches routine methods of making monoclonal antibodies with defined immunogens.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to use the teachings of the Saido A and B to generate free-end C-terminal specific AB1-40 monoclonal antibodies that do not bind the prescursor

using the conventional end-peptide immunization techniques of Saido A and B combined with monoclonal antibody technology of Goding et al because of the well established advantages of high-affinity, high specificity and unlimited supply that are central to monoclonal antibodies and Takeda et al teach that antibodies with high sensitivity and specificity for amyloid peptide, including AB1-40 are desired and Vigo-Pelfrey teaches that AB1-40 speices are soluble in CSF. One would have been motivated to make screen for free-end specific monoclonal antibodies to eliminate the residual cross-reactivity of the monoclonal antibody BA-27(a) of Takeda and because Takeda et al teach that the prior art assays lack sensitivity and specificity and that highly specific monoclonal antibodies are useful for the detection of AB1-40 and AB1-42 species *in vitro* and that unique antibodies would reduce the background and increase the sensitivity of the immunoassay for AB1-40. One of ordinary skill in the art would have a reasonable expectation of success given the demonstrated immunogenicity of the C-terminal epitope of AB1-40 as shown by Takeda and the success of Saido A for the N-terminal epitope and that Saido A teaches that similar approaches will be applicable to resolving the differential carboxy terminal processing of AB peptides. With respect to neutralizing antibody claims, the soluble form of amyloid beta is known in the art to be non-toxic (i.e. not neurotoxic) and as such any antibody that binds has neutralizing function since the anitboody binds a non-toxic form of amyloid (i.e. soluble).

Applicants again argue that there is not teaching suggestion or motivation to make antibodies to soluble beta amyloid. This is not persuasive for all the reasons already made of record. The courts have held "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come

from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). Finally, an obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). In the instant case the soluble amyloid beta peptides were known, the technology was known, it is routine to screen for antibodies with the desired specificity. Applicants argue no reasonable expectation of success using the method of Saido B to arrive at the claimed invention. This is not persuasive, Applicant's utilize similar methodology and the screening for a desired specificity is routine in this art. Absolute prediction of success not required by the art. In the instant case the soluble amyloid beta peptides were known, the technology was known, it is routine to screen for antibodies with the desired specificity.

Claims 23, 35 and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee IDS Nov 16, 2001), Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Vigo-Pelfrey et al (Journal of Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as applied to claim 14 and 24 above and further in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al (BioTechniques, 16(3):476-483, 1994) for reasons made of record in the Office Actions mailed 4-22-03, 1-26-06 and herein.

The claims are drawn to single chain antibodies that are free-N-terminal specific for AB peptide soluble in cerebrospinal fluid.

The teachings for Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Vigo-Pelfrey et al (Journal of Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as combined are set forth supra. The references as combined fail to teach single chain antibodies.

Seubert et al teaches the use of antibodies that bind AB peptides in *in vitro* or *in vivo* assays that screen for inhibitors of AB peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "… the detection techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, VL, VH, and other fragments." Seubert et al also teach that "It would also be possible to employ recombinantly produced antibodies (immunoglobulins) and variation thereof as now well described in the patent and scientific literature. See, for example EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full pargraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of a single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the free-end, N-terminal specific monoclonal antibody according to the combination of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc.,

London 1983, pages 56-97) supra, by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments including those that have been recombinantly produce that bind AB peptides are useful in a variety of detection techniques for use in screening or diagnostic assays. With respect to neutralizing antibody claims, the soluble form of amyloid beta is known in the art to be non-toxic (i.e. not neurotoxic) and as such any antibody that binds has neutralizing function since the anitboody binds a non-toxic form of amyloid (i.e. soluble).

Applicants argue since the other rejections fail for reasons previously presented, then these rejections also fail. This is not persuasive because the other rejections do not fail for reasons set forth herein and all the reasons made of record.

Claims 23, 38 and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999),Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal of Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B), Vigo-Pelfrey et al (Journal of Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as applied to claim 14 and 33 above and further in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al (BioTechniques, 16(3):476-483, 1994).

The teachings of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) in view of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal fo Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B), Vigo-Pelfrey et al (Journal of

Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) are set forth above. The references as combined differ by not teaching single chain antibodies.

Seubert et al teaches the use of antibodies that bind AB peptides in *in vitro* or *in vivo* assays that screen for inhibitors of AB peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "… the detection techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, VL, VH, and other fragments." Seubert et al also teach that "It would also be possible to employ recombinantly produced antibodies (immunoglobulins) and variation thereof as now well described in the patent and scientific literature. See, for example EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full pargraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of a single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the free-end, C-terminal specific monoclonal antibody that binds a soluble CSF amyloid beta peptide according to the combination of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) in view of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal fo Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B), Vigo-Pelfrey et al (Journal of Neurochemistry, 61:1965-1968, 1993) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) above,

by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments including those that have been recombinantly produce that bind AB peptides are useful in a variety of detection techniques for use in screening or diagnostic assays. With respect to neutralizing antibody claims, the soluble form of amyloid beta is known in the art to be non-toxic (i.e. not neurotoxic) and as such any antibody that binds has neutralizing function since the anitboody binds a non-toxic form of amyloid (i.e. soluble).

Applicants argue since the other rejections fail for reasons previously presented, then these rejections also fail. This is not persuasive because the other rejections do not fail for reasons set forth herein and all the reasons made of record.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are drawn to neutralizing antibodies that inhibit neurotoxicity and bind soluble beta amyloid. It was well established in the art at the time of the invention and admitted by Applicants in the specification that neurotoxicity was the result of fibrillar or aggregated beta amyloid and as such, an antibody that binds soluble beta amyloid cannot neutralize it's neurotoxicity becuase it is not neurotoxic in the first place. The specification does not teach that soluble amyolid is neurotoxic and as such conception of neurotoxicity associated with soluble amyloid neutralization thereof is deemed a new concept not present in the specification at the time of filing.

Applicants point to specific pages of the specification that teach that the therapeutic benefit of the antibody is to sequester the soluble amyloid beta to possibly inhibit the formation of aggregates. This is not neutralization of neurotoxicity of soluble amyloid, which is specifically claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites neutralizing antibody that binds soluble amyloid that inhibits neurotoxicity. It was well established in the art at the time of the invention and admitted by Applicants in the specification that neurotoxicity was the result of fibriallar or aggregated beta amyloid and as such, an antibody that binds soluble beta amyloid cannot neutralize it's neurotoxicity becuase it is not neurotoxic in the first place.

Status of Claims

Claims 14, 23, 24, 33, 35 and 38-40 stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
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